

UGT1A1 Polymorphism Predicts Irinotecan Toxicity: Evolving Proof

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The antineoplastic agent, irinotecan (CPT-11) is metabolized by enzymes known to exhibit polymorphic activity. Its active metabolite SN38 is glucuronidated to an inactive product by UDP-glucuronosyltransferase, UGT1A1, the isoform catalyzing bilirubin glucuronidation. Thus, glucuronidation may be an important determinant of net SN-38 concentration in bile (termed SN-38 biliary index).¹ Additional factors that determine SN-38 concentrations relative to its glucuronidated product include the activity of gut beta-glucuronidase, which affects recirculation of SN-38 and direct gut exposure to SN-38.² Recent results suggest that inter-patient variability in SN-38/SN-38 glucuronide kinetics - and possibly irinotecan toxicity - results from genetic variations in *UGT1A1* expression. For example, genetic defects in *UGT1A1* determine Crigler-Najjar and Gilbert's syndromes characterized by unconjugated hyperbilirubinemia.³ Gilbert's syndrome often remains undiagnosed and occurs in up to 19% of individuals homozygous for the *UGT1A1* (TA)⁷ allele (TA insertion in the TATAA promoter).⁴ Furthermore, since irinotecan toxicity is inversely related to SN-38 glucuronidation rate, individuals with low *UGT1A1* expression may experience severe toxicity.¹ In recent studies, decreased SN-38 glucuronidating activity has been observed in livers obtained from individuals carrying the (TA)⁷ allele.⁵ Ando et al⁶ attempted to determine whether *UGT1A1* genotype is predictive of irinotecan toxicity, in a retrospective and case-controlled study (note: there was a 3.5:1 control to case ratio). Because of small data sets analyzed and failure to control for variations in treatment patterns and other determinants of toxicity unrelated to *UGT1A1*, their conclusions are somewhat limited. Despite these limitations, it is clear that certain promoter polymorphisms were associated with severe toxicity. In their analysis of Japanese patients, multivariate analysis suggested that genotypes either heterozygous or homozygous for *UGT1A1*28* would be a significant risk factor for severe irinotecan toxicity ($P < 0.001$; odds ratio, 7.23; 95% confidence interval, 2.52-22.3). Individuals heterozygous for *UGT1A1*27* also encountered severe toxicity. One must caution how-

ever that the same genotype in another racial group may be less predictive of toxicity as other variant alleles may be more frequently expressed. Nevertheless, variable promoter TA repeats have been demonstrated to alter promoter function and transcriptional activity;⁷ this could therefore replace direct phenotyping (glucuronidation activity). However, a detailed human genotype-phenotype analysis with respect to *UGT1A1* expression and function is still needed. These studies could lead to strategies for optimizing therapy with antineoplastic agents that inherently have a low therapeutic index. In the future, *UGT1A1* genotyping may serve to spare patients from excessive toxicity resulting from therapy with irinotecan.

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